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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/749,602
Filing Date: December 31, 2003
Appellant(s): EMERY ET AL.

Christopher D. Gram

For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed appealing from the Office action mailed 20 August 2009.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

5,538,733	EMERY et al.	7-1996
5,830,479	EMERY et al.	11-1998
6,500,438	EVANS et al.	12-2002
5,339,766	PHELPS et al.	8-1994

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was

commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 34, 37, 39-43, 67-69, 83-86, 89, 91-95 and 97-102 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Emery et al. (US 5,538,733) in view of Emery et al. (US 5,830,479) in view of Phelps et al. (US 5, 339,766).

Emery et al. (US 5,538,733) discussed the problem of vaccination of young animals in that maternal antibodies present in neonates may interfere with an animal's immune response, while proposing a solution of administration of vaccines present in sustained and delayed delivery agents to young poultry between the ages of 1-90 days (see entire reference and Abstract). Emery et al. explicitly indicated that the method advantageously incorporated injection of an 'implant matrix' made of "...biocompatible, biodegradable, bioabsorbable and/or bioerodible polymeric material.." such as cholesterol and cellulosic polymers to "...release the immunogen for sustained delivery into surrounding tissue fluids over an about 1-90 day period" (see, col. 2, lines 15-55).

Emery et al. specifically indicated that "The continuous presence of a priming dose of the immunogen provides and effective way of priming a young animal so that a secondary immune

response to a pathogenic infection is stimulated substantially immediately when passive protection by maternal antibodies *against the pathogen* is no longer effective" (see paragraph bridging columns 3-4, emphasis added). Hence, it is clear that Emery et al. is stating that the immunized poultry possess the maternal antibodies against the same immunogen used to inoculate the animals including domestic fowl (see also col. 9, lines 41-49).

Emery et al. indicated that the 'time-delayed implant' "...will substantially maintain integrity of the matrix for *a desired length of time*. Preferably, the matrix will remain intact for up to about 3 weeks, or after the level of maternal antibody has significantly declined, at which time the antigen is released from the matrix." (emphasis added) Hence, the matrix is formulated for delayed delivery. Emery et al. further indicate that the matrix is formulated for delayed and sustained delivery: "The matrix may optionally be formulated to include a soluble or insoluble pore-forming agent that will dissipate from the matrix into surrounding tissue fluids causing the formation of pores and/or channels throughout the implant matrix....sodium chloride...carboxymethylcellulose" (see col. 9, lines 29-39).

A preferred immunogen for implantation disclosed by Emery et al. was siderophore receptor protein (SRP) from gram negative bacteria (see col. 7, line 50- col. 8, line 24). See also Example 2, wherein a sustained/delayed release formulation of SRP is administered to 1 day old turkey poults to establish immunity *against the SRP* indicative of an adaptive immune response. Notably,

in this Example, Emery et al. specifically indicate that a further preference for delivery time is between 1-60 days of age.

Emery et al. additionally taught the advantageous nature of administration of a booster "...to stimulate a secondary immune response in the animal," wherein the booster was an SRP. Emery et al. gave a specific example wherein a 21 day implant administered to a turkey poult is given a booster injection after the expiration of the implant, stated by Emery et al. to be 21 days after implantation, at about 28-48 days to stimulate the immune response (see col. 11, lines 1-19). This booster time disclosed by Emery et al. falls completely within the claimed booster time of 3-12 weeks (equates to 21-84 days). Serological profiles to quantify antibody titers to SRP were known at the time of Emery et al. and specifically discussed (see col. 11, lines 33-58).

Emery et al. did not specifically teach wherein the siderophore receptor was administered *in-ovo* at 'a time when maternal antibodies of the bird to the immunogen are sufficiently reduced'. Nor did Emery et al. teach the specific injection times as found in claims 39-42 and 44 or wherein a second dose of immunogen was given at 3-12 weeks post-hatching (claim 43). Emery et al. further did not teach the incorporation of porins into their vaccine.

Emery et al. (US 5,830,479) disclosed a method for immunizing poultry with a siderophore from gram-negative bacteria wherein the siderophore is enterochelin or siderophore citrate as

examples (columns 1-53, particularly col. 5, lines 29-38 and claims 1 and 3). As stated by Emery et al. "The vaccine of the present invention may be used for preventing and eliminating infections of gram-negative bacteria in poultry and other animals including humans" (col. 11, lines 9-12). Emery et al. specifically suggested sustained release administration of the vaccine (col. 11, line 15) and *in-ovo* administration in poultry: "The vaccine of the present invention may be used for preventing and eliminating infections of gram-negative bacteria in poultry and other animals, including humans....may be delivered to the animal, for example, by...egg inoculation (i.e., poultry)...by known techniques in the art...the vaccine contains an amount of a siderophore receptor protein to stimulate a level of active immunity in the animal to inhibit and/or eliminate gram-negative bacterial pathogenesis and/or sepsis" (col. 11, lines 10-21). Emery et al. specifically taught that "The protein may also be incorporated into a carrier which is a [*sic*] biocompatible and can incorporate the protein and provide for its controlled release or delivery, for example, a sustained release polymer such as a hydrogel, acrylate, polylactide, polycaprolactone, polyglycolide or copolymer thereof...an example of a solid matrix for implantation into the animal and sustained release of the protein antigen into the body is a matabolizable matrix, as described...in US ...4,452,775 (Kent)" (col. 11, lines 27-36). Emery et al. also taught the advantageous use of a booster vaccine given "21-28 days after the first injection" and the use of adjuvants such as porins from gram negative bacteria for administration along with SRP's (see, col. 7, line 50-col. 8, line 9). Emery et al. offered that the amount of vaccine was varied in order to achieve optimal vaccination (see col. 11, line 49- col. 12, line 6).

Phelps et al. (US 5, 339,766) disclosed a method for introducing material into poultry eggs during early embryonic development which included injection of a therapeutic substance contained within a biodegradable matrix such as polylactide polymers (lactides/glycolides) directly into the developing bird egg. Materials intended for delivery included "vaccines, vitamins, antibiotics hormones, enzyme inhibitors, peptides, cells, DNA and other therapeutic molecules" (col. 3, lines 33-36). Phelps et al. discussed that, "Eggs treated by the method of the present invention are preferably fertile eggs which may be in any period of incubation, from early to late... " (col. 4, lines 15-18). Phelps et al. further explained that "Such beneficial effects included increased growth, disease resistance due to in ovo vaccination, increased percentage hatch of multiple incubated eggs, and otherwise improved physical characteristics of hatched poultry" (col. 1, lines 20-24).

One of ordinary skill in the art would have been motivated to administer a sustained-release formulation *in ovo*, to a bird (i.e., poultry such as chicken) wherein the formulation comprised a siderophore receptor such as enterochelin, and wherein the sustained-release formulation was sustained until the hatching of the bird (i.e., 1-60 or 1-90 days post-hatching) in order to increase the bird's immune system to foreign disease causing bacteria. It was clear from the prior art that siderophore receptors from gram-negative bacteria were known to vaccinate birds, and suggested for use *in-ovo* by Emery et al. '479. Further disclosed by Emery et al. as well as Phelps et al. were suitable mediums and sustained release biocompatible matrices for *in-ovo* injection of vaccines. The ordinary artisan would have recognized, in view of Emery '773 that sustained release of SRPs to young poultry or poultry embryos (*in-ovo*) would need to be formulated to release the SRPs at a time that the immunogen is "sufficiently reduced so that the birds are capable of mounting an

adaptive immune response". This knowledge in the art of poultry immunization is made perfectly clear by Emery '773 who teach that maternal antibodies to the antigen must be low enough for the birds to amount an immune response. The teachings of '773 are clear that maternal antibodies are present in the embryo and wane only after the bird is hatched. It is clear from the teachings of the references as a whole, that the Emery et al. patent '773 although not teaching egg inoculation of their sustained/delayed release matrix SRP vaccine is cured by the subsequent Emery '479 patent which clearly suggests SRP inoculation in-ovo (in birds) and further suggests the advantageous addition of porin as an adjuvant, into an egg to vaccinate young poultry.

While Emery '479 did not explicitly teach wherein the *in-ovo* vaccination would be carried-out via use of sustained/delayed release matrices, one or ordinary skill in the art drawing from the teachings of Emery et al. '733 would have been motivated to use sustained/delayed release matrices for *in-ovo* injection in order to sustain delivery of SRP's *in-ovo* but also to formulate the vaccine in such a manner as to release the SRP entirely at a time when maternal antibodies are sufficiently low so as to allow the bird (after hatching) to produce a full immune response to the SRP.

In-ovo vaccination techniques as claimed were known and well-utilized and rendered obvious at the time the Invention was made as evidenced by Phelps et al. . Emery et al. '773 and Emery et al. '749 together taught optimal times for vaccinating young poultry at a time when maternal antibodies were reduced in order for the bird to mount an immune response; Emery et al. '773 teaching specific times advantageous to administer such a vaccine which included SRP when maternal antibodies to SRP were 'sufficiently reduced': the 'time-delayed implant' "...will

substantially maintain integrity of the matrix for *a desired length of time*. Preferably, the matrix will remain intact for up to about 3 weeks, or after the level of maternal antibody has significantly declined, at which time the antigen is released from the matrix." (*Id.*, emphasis added) Considering the evidence as a whole, it is the opinion of the Examiner that at the time the invention was made, the claimed invention was an obvious modification of known methods and that the modifications within the claims which differ with respect to the prior art teachings could have been achieved through routine experimentation applying known techniques which were readily available at the time the invention was made.

Time delayed/sustained matrices for delivering SRP to poultry were known in the art at the time the invention was made and known to be manipulated to release SRP at a desired time. The results achieved by both Emery et al. patents include successful vaccination of young poults anywhere from injection at one day (with the sustained delivery matrix of Emery et al. '773, formulated to release at 21 or 60 days), three weeks (see Example 3, Emery et al. '479) and six weeks (Emery et al. '479).

There is no explicit time indicated in the prior art nor the Instant specification of 'until the maternal antibodies in a bird hatching from the egg are reduced so that the bird is capable of mounting an adaptive immune response to the immunogen' because this time would vary from bird to bird. Hence the reason for the delayed/sustained release formulations of both Emery et al. patents. Such a formulation intended for sustained/delayed release would provide continual vaccine delivery over a desired amount of time in order to successfully vaccinate young birds. The ordinary

artisan, having the knowledge offered by the combination of cited references, would have had a reasonable expectation of success in adopting such knowledge to inoculate SRPs *in-ovo* prior to hatching at the times recited by the claims. This aspect of the claimed invention is obvious in the opinion of the Examiner because the prior art, although not knowing exactly when maternal antibodies (to the antigen) would be sufficiently reduced so that a bird was capable of mounting an immune response (due to the fact that each bird will possess different amounts of maternal antibody to any given antigen as discussed by the Examiner above), disclosed optimal windows of time for release of antigens such as SRP; e.g., between 1-90 days or 1-60 days (*Id.*).

Claims 34-44, 67-69, 71-82, and 84 –102 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Emery et al. (US 5,830,479) in view of Phelps et al. (US 5, 339,766) in view of Emery et al. (US 5,538,733).and further in view of Evans et al. (US 6,500,438 B2).

The teachings of Emery et al. '749, Emery et al. '773 and Phelps '776, were discussed *supra*. None of these references specifically taught t the specific injection protocols as recited in claims 35, 36, 38 and 44.

Evans et al. (US 6,500,438 B2) taught a method for *in ovo* vaccination of chickens with *E. sporozoites* via injection, wherein the injection was preferentially performed in the final quarter of incubation or specifically at day 18 of incubation, however would have been effective during any time of incubation (col. 2, lines 1-6, col. 3 lines 25-27 and Example 1).

Hence, although the prior art did not teach a specific embodiment where SRP was injected into bird eggs at the claimed injection times as required by claims 35, 36, 38 and 44, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A. It is clear from the prior art teachings as a whole that the sustained/delayed release matrices including SRP and advantageously including porins as an adjuvant to the SRP vaccine were formulated to release during a time that maternal antibodies to the vaccine were sufficiently reduced in order for the chick to produce antibodies to the vaccine. Such matrices were well-known in the art and producing such compositions was within the skill level of the ordinary artisan at the time the invention was made. *In-ovo* injections to produce an immune response were further known in the prior art to be carried out within the time frames specified by the claims. The knowledge gleaned from the prior art concerning vaccination with SRPs in sustained/release formulations in birds such as poultry, coupled with the knowledge that Emery et al. showed successful vaccination of sustained/release SRPs whereby the release of the antigen was set for 21 or 60 days (Emery et al. '733) would have provided the ordinary artisan with the requisite knowledge that *in-ovo* injection of SRPs would have been successfully carried out when administered in a sustained/release matrix set to release after hatching at times already indicated by the prior art as being times that maternal antibodies to the antigen were sufficiently low (so the bird will produce an immune response to the antigen). Having the knowledge presented by the prior art documents, the ordinary artisan could chose specific times for injections such as the fourth quarter of an egg and produce SRP vaccines in sustained/release

matrices to release during any time disclosed by the prior art as being an optimal window whereby the birds would possess maternal antibodies in quantities low enough that the bird would mount an immune response (e.g., 1-90 days or 1-60 days or specifically 21 or 60 days as disclosed by the prior art). [If]… there are [a] finite number of identified, predictable solutions, [a] person of ordinary skill in art has good reason to pursue known options within his or her technical grasp, and if this leads to anticipated success, it is likely product of ordinary skill and common sense, not innovation *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 U.S. 2007.

The Supreme court has acknowledged:

> When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. **If a person of ordinary skill can implement a predictable varition..103 likely bars its patentability**…if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond that person's skill. A court must ask whether the improvement is more than the predictable use of prior-art elements according to their established functions…
>
> …**the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results** (see *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 U.S. 2007) emphasis added.

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

(10) Response to Argument

Pertaining to the rejection of Claims 34, 37, 39-43, 67-69, 83-86, 89, 91-95 and 97-102 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Emery et al. (US 5,538,733) in view of Emery et al. (US 5,830,479) in view of Phelps et al. (US 5, 339,766), Appellants proffer the following arguments:

Appellants commence their arguments by reciting the statute under 35 USC 103(a) and providing an expert from *KSR International Co. v. Teleflex*: "...If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability." (p. 5, Appeal Brief). Appellants assert that a person skilled in the art could not have predictably manipulated the art to arrive at Appellants' claimed invention (pp. 5-6, Appeal Brief).

Appellants' remarks on page 7 of the Appeal Brief are a general reiteration of more specific statements made by the Examiner in the rejection and are not disputed by the Examiner.

Appellants specifically argue that the Examiner has failed to recognize that the subject matter in claim 34 "reflects more than simply combining familiar elements according to known methods to yield predictable results." (p. 8, Appeal Brief). Appellants support their contention by asserting the following statements:

> Appellants submit that prior to Appellants disclosure, one skilled in the art could not have combined the teaching of the '733 patent, '479 patent, and the '766 patent as suggested by the

> Examiner and predictably arrived at the method of claim 34. In particular, the portion of the '479 patent that the Examiner asserts teaches delivery of SRPs *in ovo* does not account for the presence of maternal antibodies against the selected immunogen in the unhatched egg. Moreover, one skilled in the art would have understood that the immunological environment of the newly hatched bird and a soon-to-be-hatched egg are different enough that the skilled person could not predictably extrapolate the teaching of the '733 patent to in ovo administration of the sustained release implant.

However, Emery '733 specifically teaches that maternal antibodies are present *in-ovo*:

> In mammals, a fetus receives maternally-synthesized antibodies while in utero which confers passive protection to the fetus. In the avian species, immunity is transferred from the hen via the egg, and the progeny in the first few months of life are protected against toxins, viruses and pathogenic bacteria. the levels of these maternal antibodies gradually decline as the newborn begins to synthesize its own antibodies.

Thus, it is clear that in Example 2, wherein Emery et al. '733 inoculate the poults, that maternal antibodies are present, as they are present in the egg.

Appellants argue:

> The method of claim 34 allows those in the poultry industry to vaccinate a generation of birds while the birds are relatively easy to handle - i.e., prior to hatching. Thus, one can protect an entire generation of birds while administering vaccinations to each individual at one time. The desire to protect a generation of eggs in this way faces at least two significant challenges, each of which is explained in Appellants' specification.
>
> First, in the first few weeks of life a newborn chick, poult, duckling or other avian hatchling (hereinafter, collectively "chick" for brevity) is relatively incompetent at producing antibodies in response to antigenic stimuli. During this period, a significant amount of resistance to infectious diseases is provided by passive immunity derived from maternal antibodies of the hen. Passive immunity can be transferred from the hen to the chick in ovo. IgY antibodies are sequestered from the hen's serum, secreted in the ovary, and incorporated into the yolk before ovulation. Of course, only IgY antibodies against immunogens to which the hen has been exposed recently enough to still have circulating IgY antibodies in her serum can be sequestered and secreted to the ovary. Thus, with respect to a specific immunogen - e.g., a selected SRP from a certain gram negative bacterium - while one hen may have been exposed to the immunogen recently enough so that her circulating IgY against the immunogen is at its peak, another hen may have been exposed so recently (e.g., less than eight days) so that circulating IgY against the immunogen is nonexistent or less than full strength, while another hen may have been exposed to the immunogen so long ago (e.g., more than six weeks) that circulating IgY against the immunogen has waned, while yet another hen may never have been exposed to the immunogen and, therefore, have no circulating IgY against the immunogen. One

> important implication of this is that the transfer of maternal antibodies to eggs is not consistent across hens of a flock - i.e., each hen may differ in not only the qualitative ability to provide maternally- derived antibodies against a selected immunogen, but also the quantity of maternally-derived antibody against a selected immunogen. Thus, within any given population of egg-laying hens, one expects to find varying levels of serum antibody raised against any particular immunogen. This variation within the flock is passed to the eggs, which results in variation of the amount of maternal antibody against any particular immunogen among the eggs of a given generation - variation that is directly correlated with the varying amounts of serum antibody against the particular immunogen present in the flock of egg-laying hens at the time that the hens lay eggs.
>
> Maternally-derived antibodies are stored in the yolk until the later stages of embryonic development when they are absorbed by the embryonic membranes and transferred to the circulation of the chick to provide passive immunity. Maternally-derived antibodies provide immunological protection of the newly hatched chick during the period before the chick's own immune system can actively produce antibody against immunogens of pathogens. The amount of maternally-derived antibody against a selected immunogen influences the duration of passive immunity conferred to the newly hatched chick.
>
> However, the presence of maternally-derived antibodies can also interfere with the ability of the young bird to actively respond to an immunogen and, instead, induce immune tolerance. Immune tolerance to a foreign antigen can occur when a subject is exposed to a foreign antigen under conditions that elicit specific unresponsiveness to the foreign antigen rather than an adaptive humoral immune response to the antigen. In other words, under some circumstances, exposure to a foreign antigen does not necessarily result in the challenged subject mounting an adaptive immune response, but instead results in the subject's immune system perceiving the foreign antigen as "self' and establishing antigen-specific immune non-response. (pp. 8-10, Appeal Brief, emphasis in Appellants' original remarks)

However, Appellants' arguments regarding the fact that an immune response to the antigen may not have occurred due to *in-ovo* vaccination of chicks using sustained release would be an exception to the rule and is not a persuasive argument. The skilled artisan would have understood at the time the invention was made that vaccinations are not 100% successful. Based upon the combined teachings of the prior art however, the ordinary artisan would have had a reasonable expectation of success: the prior art already recognized the use of SRPs for vaccination into poults as well as *in-ovo* via use of sustained delivery matricies. It is evident upon reading the references in combination; that the ordinary artisan, considering the successfulness of vaccination using SRP proteins in young chicks, that delivery of SRP's comprising a delayed release matrix, which was

already taught by the prior art, to release at times already known to be successful for vaccinating young birds such as one day old poults would have been obvious at the time the invention was made. In other words, it would have been obvious to formulate vaccines containing SRPs with sustained/release matricies to deliver the SRPs at a desired time, such as one day (or 1-90 or 1-60 or 21 or 60 days as reported by the prior art) after hatching. This technology was already known and readily-available to the ordinary artisan working in the art at the time the Invention was made.

Appellants' assertions are unsubstantiated and found unpersuasive to the Examiner in view of the prior art teachings. Emery '733 explicitly taught *in-ovo* vaccination using sustained/delayed release of SRP antigen to vaccinate poultry. Although there is no specific example of where Emery performed *in-ovo* vaccination; there is an explicit suggestion for the ordinary artisan to perform *in-ovo* vaccination by Emery et al. and further, *in-ovo* vaccination techniques were well-known and conventional in the art at the time the Invention was made. While Appellants point to unknown parameters and unpredictability with regard to *in-ovo* vaccination, it is the opinion of the Examiner that the level of unpredictability in the Instant case does not rise to the level of patentability (of the claimed invention) considering that the prior art explicitly suggested *in-ovo* vaccination of birds, specifically taught the delayed/sustained release times of the claims and specifically taught the use of SRP proteins for these purposes.

Additionally, there is no indication in the prior art that *in-ovo* vaccination with SRP proteins specifically would be unpredictable. The teachings presented by Emery '733 teach that *in-ovo* administration of the SRP protein could be carried-out by known techniques in the art (col. 11,

lines 10-21). One seeking specific techniques on *in-ovo* injection would have sought out conventional in-ovo injection techniques such as the techniques described by Phelps et al. Emery et al. '733 additionally taught that maternal antibodies decline as newborn chicks begin to synthesize their own antibodies:

> To properly protect a herd or flock of animals from bacterial and viral infections, it is important that the animals maintain a level of immunity against a pathogen at the point when effective passive immunity from circulating maternal antibodies is lost. In mammals, a fetus receives maternally-synthesized antibodies while in utero which confers passive protection to the fetus. In the avian species, immunity is transferred from the hen via the egg, and the progeny in the first few months of life are protected against toxins, viruses and pathogenic bacteria. The levels of these maternal antibodies gradually decline as the newborn begins to synthesize its own antibodies.

Example 2 of Emery et al. '733 (col. 12- col. 15) provides the ordinary artisan with the knowledge that one day old turkey poults administered a 60 day release formulation of SRP's were capable of mounting an immune response in the presence of maternal antibodies. Figure 4 provides indication that turkey poults provide an adaptive immune response when the immunogen (in this case BSA) with a 21 day implant. Thus, the poults must have had an amount of maternal antibodies that was sufficiently low enough that the poults would be capable of mounting an immune response. Having this knowledge, and taking the suggestion of Emery '479 patent to deliver SRPs *in-ovo*, the ordinary artisan could have predictably created a vaccine to inoculate poultry eggs such as turkey eggs in the fourth quarter of an incubation of an egg to deliver the immunogen (via delayed release using appropriate matricies) at a time such as approximately 21 days or 60 days after hatching since these methods were already proven successful.

Further, while Appellants assert that the unpredictability of in-ovo vaccination arises due to the contention that a sustained release of antigen, the primary objective of Emery '733 is to provide antigens such as SRP in a sustained and delayed matrix in order to gradually release SRP as a priming dose:

> These and other objects are achieved by the present invention which is directed to a method of priming an immune response in a young animal by administering a biocompatible and non-toxic solid phase implant containing an immunogenic agent. The implant is administered to the animal at about 1-90 days of age in the presence of circulating maternal antibodies, and provides extended sustained delivery of a priming dose of the immunogenic agent into surrounding tissue fluids in the presence of circulating maternal antibodies. A preferred application is the administration of the implant to a one-day old animal.
>
> Advantageously, the present method provides a system for delivering a priming dose of an immunogen to a young animal in the presence of circulating maternal antibodies over an extended time so that the animal will produce a secondary active immune response substantially immediately upon contact with the immunogen when passive protection is no longer provided by circulating maternal antibodies. The priming dose of the immunogen released from the implant is effective to elicit a secondary immune response in the animal to increase the anti-immunogen antibodies to an antibody titer of about 10-1000, or an about 5-100 fold increase in antibody titers.

Therefore, the prior art indicates that the sustained release in the presence of maternal antibodies is not deleterious to producing an overall immune response and subsequent vaccination. One would thus predict that in-ovo injection of SRP in a sustained/delayed matrix formulated to deliver SRP at a time when maternal antibodies were sufficiently low so the bird is capable of mounting an immune response would successfully provide for an immune response (i.e., successful vaccination).

Thus, it is the opinion of the Examiner that the subject matter of the claims is predictable based upon the combination of the prior art. Although Appellants attempt to convey the unpredictability of vaccination of poultry eggs, it is the opinion of the Examiner that one of ordinary skill in the art would have possessed a suitable amount of knowledge to use the claimed methods based upon the combination of the prior art. It is the opinion of the examiner that the prior art motivates one not to vaccinate in the egg *per se*, but to inject eggs with the SRP antigen in a sustained/delayed release matrix formulated to deliver the SRP until a time when maternal antibodies are sufficiently low so that the bird will mount an immune response. Thus, while sustained release would occur *in ovo*, such sustained release would act as a priming dose of immunogen "so that the animal will produce a secondary active immune response substantially immediately upon contact with the immunogen when passive protection is no longer provided by circulating maternal antibodies" (*Id.*) That time of contact being upon delayed release which does not occur until a time when it was known that the maternal antibodies were reduced enough so the bird could mount an immune response. Having the knowledge presented by both Emery et al. patents, one would not proceed with inoculation of an egg in order to vaccinate the egg fully due to the fact that maternal antibody titers would be too elevated (*Id.*).

While there is an amount of unpredictability regarding the immune functions of poultry embryos, if there were unpredictability in the art regarding this immunity, the unpredictability still exists in this application because there is no indication in the Instant specification that Appellants have achieved any result which was not already expected by the prior art. Appellants' only example regarding *in-ovo* inoculation merely quantitated live births and evaluated the injection sites.

Appellants did not state exactly how the biocompatible matrix was prepared for this example (i.e., a determined release time), did not measure the maternal antibody titers of the eggs, did not measure antibody titers of the chicks after hatching and thus did not evaluate the overall success of a 20 day old egg vaccination. Nor did Appellants provide any comparative data which would demonstrate that an egg at day 20 of incubation would provide for any result which would not be expected by the prior art (i.e., vaccination). It appears that this example, Example 4 in the Specification; the only example in the Specification pertaining to *in-ovo* vaccination; was set forth to assess the toxic nature of the injection itself, as there is no subsequent data at all concerning these inoculated eggs. Hence, even considering if there is unpredictability in the art with regard to vaccination of poultry eggs 1) the prior art suggested *in-ovo* vaccination of SRP proteins using sustained/delayed release matricies, 2) the prior art taught the advantageous nature of delivering SRP proteins in biocompatible sustained/delayed release matricies to deliver SRP proteins to poults when decreased maternal antibodies were present and 3) *in-ovo* vaccinations were routine in the art and 4) *in ovo* vaccinations were successfully achieved by injecting antigens at the times recited by the claims.

Hence, if the Examiner had reason to believe that the claimed composition was unpredictable, the claims themselves would be rejected under 35 USC 112 First paragraph, because if a large degree of unpredictability existed, Appellants' specification would not cure this deficiency considering the lack of teachings in the Specification with regard to *in-ovo* inoculation. Nevertheless, it is taken from the prior art as a whole that the claims are enabled because the prior art already taught successful vaccination of young poultry with SRP proteins via use of a biocompatible matrix designed to provide sustained/delayed release until a time when maternal

antibodies were sufficiently reduced so the bird could mount an immune response to the immunogen (SRPs) and because SRPs delivered in such matricies were specifically suggested for in-ovo administration. Considering the breadth of information concerning poultry vaccination with SRPs, the prior art is deemed enabling and the artisan would have had a reasonable expectation of success in combining the teachings of the prior art thereby resulting in the claimed invention.

The variance between maternal antibodies in any one-given hen as argued by Appellants (pp. 8-9, Appeal Brief) would be true of any flock of birds but it is the opinion of the Examiner that this knowledge does not detract from the fact that the prior art successfully inoculated birds with sustained/delayed release of SRP proteins. One of ordinary skill in the art reading either Emery et al. patent would be apprised of the usefulness of such a sustained/delayed release vaccine, even though it would be accepted that not all birds will be fully vaccinated.

Appellants further argue:

> In summary, prior to Appellants' invention, those in the poultry industry wanting to vaccinate a new generation of birds must weigh the following challenge. To ensure that all of the chicks are vaccinated at a time when the chicks are able to mount an adaptive immune response to immunogens in the vaccine, one must wait until (a) each chick's immune system is competent to raise an adaptive immune response to the immunogens in the vaccine, and (b) maternally-derived antibodies to the selected immunogens have waned so as not to interfere with the ability of the chick's immune system to recognize the vaccine immunogens. However, this option leaves certain chicks - those chicks without maternally-derived passive immunity to the particular immunogen - unprotected and at risk to infection because (a) the qualitative existence of, and (b) the amount of maternally-derived antibodies against a particular immunogen varies from egg to egg because the fact, extent, and timing of exposure of the hen to a pathogen harboring the particular immunogen varies from hen to hen.
>
> The '733 patent suggests providing the chick with a sustained release implant that releases immunogens over time so that the immunogen will be present when (a) the chick's immune system is competent to raise an adaptive immune response and (b) maternally-derived antibodies to the selected immunogens have waned so that the chick's immune system can take over. The Examiner errs in concluding that the method of claim 34 represents little more than

administering the sustained release implant of the '733 patent in ovo rather than' post-hatch. So why wouldn't the skilled person modify the teaching of the '733 patent to administer the implant in ovo? After all, eggs are easier to handle than even one-day old chicks and methods for introducing materials into eggs were known as of the filing date of the '733 patent. M.P.E.P. §2145(X)(D) hints at the answer, stating

> The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. In re Hedges, 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986) (Applicant's claimed process for sulfonating diphenyt sulfone at a temperature above 127°C was contrary to accepted wisdom because the prior art as a whole suggested using lower temperatures for optimum results as evidenced by charring, decomposition, or reduced yields at higher temperatures.).

Furthermore, "[k]nown disadvantages in old devices which would naturally discourage search for new inventions may be taken into account in determining obviousness." United States v. Adams, 383 U.S. 39, 52, 148 USPQ 479, 484 (1966).

Additionally, the U.S. Supreme Court in KSR approvingly referred to the Court's U.S. v. Adams decision as follows: "The Court relied upon the corollary principle that when a prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious." 82 USPQ2d, 1395 (emphasis added). Simply put, the immunological environment of the unhatched embryo is known to those skilled in the art to be sufficiently different from the one-day old chick that (a) one could not predict that sustained release of immunogen in ovo when maternally-derived antibodies to the immunogen are present would induce a protective adaptive immune response in the chick once hatched, and (b) the prior art teaches away from sustained release of the immunogen in ovo when maternally-derived antibodies to the immunogen are present because of the risk of inducing exactly the opposite response: immune tolerance. (pp. 10-11, Appeal Brief)

Simply put, the immunological environment of the unhatched embryo is known to those skilled in the art to be sufficiently different from the one-day old chick that (a) one could not predict that sustained release of immunogen in ovo when maternally-derived antibodies to the immunogen are present would induce a protective adaptive immune response in the chick once hatched, and (b) the prior art teaches away from sustained release of the immunogen in ovo when maternally-derived antibodies to the immunogen are present because of the risk of inducing exactly the opposite response: immune tolerance.

The issue in the Appeal is not whether it was technically possible to administer a sustained release implant *in ovo*. The issue is whether the skilled person would have done so and been able to predict that an adaptive immune response would result. Appellants submit that the skilled person could not predict that an adaptive immune response against immunogens in the implant would result. Moreover, the prior art teaches the skilled person that sustained release vaccination *in ovo* when maternally-derived antibodies against the immunogen are present may induce immune tolerance.

Many of the conditions under which immune tolerance may be induced are present in the circumstance of *in ovo* vaccination as recited in claim 34. (See, Microbiology fourth edition, Davis et al. eds., 1990, J.B. Lippincott Co., Philadelphia, Pennsylvania, pp. 381- 382.). For example, the selected immunogens, SRPs, are monomeric antigens, not aggregated; sustained release implants are more similar to intravenous administration than injection into tissue; and *in ovo* administration necessarily results in vaccination of the embryo rather than adult. So, one skilled in the art would recognize that vaccinating embryos using sustained release of SRPs harbors the risk of inducing immune tolerance to the SRPs in the vaccine rather than raising adaptive

> immunity against the SRPs. Many of these conditions are present whether the sustained release implant is administered at one day of age (as in the '733 patent) or in ovo, as in the present claims. (pp. 10-12 Appeal Brief).

However, again, Appellants' statements regarding the unpredictability regarding the claimed invention are unsubstantiated and in the opinion of the Examiner, are not found convincing. There is no evidence within the prior art or the Instant specification which provides indication that *in-ovo* injection of SRPs in a sustained/delayed matrix would as unpredictable as Appellants assert and that the unpredictability occurring with *in-ovo* inoculation could not be cured with techniques and manipulation of inoculation protocols readily available to those of ordinary skill at the time the invention was made. Further, while Appellants argue that the immunological environment of the unhatched embryo is known to those skilled in the art to be sufficiently different from the one-day old chick and thus one could not predictably carry out the claimed method; Appellants' claims are not directed toward a newly fertilized egg, but rather, are directed toward egg inoculation in the fourth quarter, substantially close to hatching.

Appellants' contention that the prior art teaches away from the claimed invention is respectfully not accepted by the Examiner. Again, sustained release matricies were demonstrated effective even in the presence of maternal antibodies as they were acting as a primer (*Id.*). Thus, the ordinary artisan would have had a reasonable expectation of success that *in-ovo* delivery of an SRP-containing implant formulated for sustained/delayed release of the SRP until a time when maternal antibodies were sufficiently low so as the bird could mount an immune response would result in vaccination of the bird to SRP.

Appellants further argue:

The difference between vaccinating an egg by sustained release of a selected immunogen from a biocompatible implant at one day of age versus injecting the biocompatible implant *in ovo* - and a compelling reason why one skilled in the art would not extend the teaching of the '733 patent to in ovo delivery- is that the risk of inducing immune tolerance to the immunogen is greater when the biocompatible implant containing the immunogen is delivered in ovo compared to the biocompatible implant being delivered after hatch. In other words, the multifactorial risk of inducing the exact opposite of the intended immunological response is magnified when the sustained release implant is administered in ovo rather than after hatching. One reason for the increased risk of inducing immune tolerance when the biocompatible implant is injected in ovo is the different amounts of- and the corresponding effects of the different amounts of- circulating maternal antibody in the embryo versus in the newly-hatched chick.

Claim 34 recites that the egg into which the biocompatible implant is injected comprises maternal antibody to the selected immunogen. Recall that across a generation of eggs, the qualitative presence of maternally-derived antibodies against a selected immunogen and the quantitative amount of maternally-derived antibodies against a selected immunogen vary from egg to egg. Prior to hatch, some of the maternal antibodies circulate in the embryo but most remain sequestered in the yolk. At hatching, however, the yolk is fully absorbed and the maternal antibodies from the yolk are fully absorbed into the circulation of the chick. Thus, the chick - but not the embryo - has the full passive immunization benefit of the maternal antibodies, which may or may not include maternal antibodies against a particular immunogen. Consequently, the circulating maternal antibody environment is very different in the embryo than in the newly-hatched chick and this difference influences the risk of inducing immune tolerance.

The difference in the circulating maternal antibody environments present in the embryo and the newly-hatched chick dictate the different immunological responses that one skilled in the art would have expected to vaccines administered by sustained release implant in ovo versus post-hatch. As just explained, a day-old chick possesses the full amount of maternal antibody in circulation, including any maternal antibody specific to the selected immunogen. When a day- old chick is vaccinated with a biocompatible implant providing sustained release of the selected immunogen, maternal antibodies against the selected immunogen - if present at all - clear the immunogen from the chick's circulation without involving the chick's immature immune system, thereby reducing the risk of inducing immune tolerance to the selected immunogen. In contrast, when a biocompatible implant is provided in ovo, the level of maternal antibody absorbed by the embryo - e.g., at day 20 of incubation as described in Example 4 - is incomplete and, as a consequence, the immunogen is less likely to be cleared by maternal antibodies against the immunogen. As a result, the embryo is more likely to be exposed to the immunogen. Because of the immaturity of the embryo's immune system, the embryo's exposure to the immunogen presents the risk that the embryo will recognize the immunogen as "self" rather than "foreign" and, as a consequence, the embryo is at risk for developing immune tolerance to the immunogen in the biocompatible implant rather than adaptive immunity against the immunogen.

At least two factors put the embryo at greater risk for inducing immune tolerance to the selected immunogen than a newly-hatched chick receiving the very same sustained release implant. First, the embryo's immune system is less mature and, therefore, is less capable of raising an adaptive response to a foreign antigen and is, therefore, more susceptible to inducing immune tolerance to the foreign antigen. Second, the immune system of an embryo is less protected from the foreign antigen by maternal antibodies, if present at all, than the immune system of a day-old chick. Each factor, alone, is sufficient to render the effect of administering he sustained release implant to an embryo unpredictable. Taken together, however, one skilled in

> the art could not have predicted that vaccinating eggs using the recited implant would provide effective vaccination rather than inducing immune tolerance.
>
> Thus, prior to Appellants' disclosure, it was unpredictable whether injecting a biocompatible implant containing a selected immunogen into an egg that possesses maternal antibody against the selected immunogen could induce an adaptive immune response against a selected immunogen or, alternatively, whether doing so would induce immune tolerance to the selected immunogen.
>
> Because the combination of the '733 patent and the °479 patent fails to provide one skilled in the art with a reasonable expectation that injecting a biocompatible implant containing a selected immunogen *in ovo* would induce an effective adaptive immune response rather than inducing immune tolerance, the combination does not help establish a prima facie case of obviousness against claim 34. Nothing in the '766 patent cures this deficiency in the combined teachings of the '733 patent and the '479 patent (pp. 12-14, Appeal Brief, emphasis in Appellants' remarks).

However, while there may be a difference between vaccinating an egg by sustained release as compared to a one day old poult, Appellants have not disclosed or discussed the specific differences. While Appellants state that the risk of inducing immune tolerance is greater when delivered *in ovo* as compared to vaccination in a bird, Appellants have provided no indication of how much greater the risk would be. Appellants' contention that *in-ovo* administration of SRP in a sustained/delayed release delivery matrix would risk immune tolerance is unsubstantiated. Further, considering *arguendo* that there were a risk, it is the opinion of the Examiner, based upon the success of vaccination of day-old turkey poults with SRPs in a sustained/delayed release matrix in the presence of maternal antibodies, it would have indicated to the ordinary artisan that injection of SRP in-ovo would have also been successful. To reiterate from above, the ordinary artisan would not have expected every vaccination to be successful, however, judging from the success rate in the prior art, the ordinary artisan would have had a reasonable expectation that *in-ovo* vaccination would have been beneficial and successful to a large extent. The combination of prior art, the Emery et al patents in particular as these are the closest prior art to Appellants' claimed invention , while expressing the unpredictability of delivering vaccines such as SRPs to young poultry due to the presence of maternal antibodies and subsequently overcoming this problem by producing a

sustained/delayed release matrix containing the vaccine such as SRP in order to deliver the vaccine at a time when maternal antibodies were sufficiently reduced so the bird could elicit an immune response to the SRP, stated nothing with regard to problems in the prior art faced with *in-ovo* vaccination of SRP proteins. The remainder of Appellants' arguments are again, unsubstantiated and unverified. The Examiner is not convinced by Appellants' statements because there is no evidence within the prior art, nor the Instant specification that Appellants have invented a method which had been proven unsuccessful or unpredictable in the past.

Appellants' Specification reiterates previous problems in the art concerning vaccination of poultry which were already solved by the Emery et al. Patents. Appellants further provide indication that *in-ovo* administration is "subject to the interfering affects of circulating maternal antibodies." (p. 4, Specification) (e.g., Appellants indicate when IgG is present in the yolk during incubation). However, after this disclosure, the remainder of the Specification essentially reiterates what is already taught in the prior art and what was already known regarding delivery of SRP proteins and formulation of suitable sustained/delayed release matricies containing said proteins and what was already known generally regarding *in-ovo* injection of vaccines. The sustained/delayed release formulations as disclosed by Appellants are the same formulations as disclosed by the prior art. Appellants discuss "a delayed release implant provides a burst release of the immunogen at a predetermined time post hatching. The time at which maternal antibody concentrations decrease can vary between birds. However, generally, maternal antibody concentrations decrease at about 7 to 28 days post hatching. Hence, to provide the immunogen at a time when maternal antibodies are sufficiently reduced to provide an immunizing effect, typically the immunogen of a delayed release

implant is released at about 7 to 21, preferably about 14 to 28 days post hatching." (pp. 23-24, Specification). It is the opinion of the examiner that the information given here is inferred by the prior art; this was material already known as disclosed by the combination of the cited prior art references. There is no disclosure of the extent of unpredictability concerning *in-ovo* inoculation currently proposed by Appellants in their arguments. Additionally, there is no disclosure that the injection times as claimed would provide for any effect which would not be predicted from the prior art.

Appellants argue:

> Because the combination of the '733 patent and the '479 patent falls to provide one skilled in the art with a reasonable expectation that injecting a biocompatible implant containing a selected immunogen in ovo would induce an effective adaptive immune response rather than inducing immune tolerance, the combination does not help establish a prima facie case of obviousness against claim 34. Nothing in the '766 patent cures this deficiency in the combined teachings of the '733 patent and the '479 patent.
>
> The Examiner errs in focusing on whether SRPs were known to be immunogens (yes, see, e.g., the '479 patent), whether sustained release of SRPs was known (yes, see, e.g., the '733 patent), and whether Implanting materials in ovo was possible (yes, see, e.g., the '766 patent). The Examiner errs by ignoring - and what one skilled in the art was unable to predict prior to Appellants' disclosure - the biological consequence of providing a sustained release implant in ovo to eggs that contain maternally-derived antibodies to an immunogen released by the implant.
>
> In responding to Appellants' arguments in the Final Office Action (pages 12-21), the Examiner errs by confusing the teachings provided in the cited documents. The Examiner states, "[T]he prior art already recognizes the use of SRPs for vaccination into poults as well as in-vivo [sic] via use of sustained delivery matrices." (Final Office Action, page 13). The prior art fails to recognize the use of SRPs for vaccination in ovo using sustained delivery matrix implanted into eggs having maternally-derived antibodies to an immunogen released by the implant. (pp. 14-15, Appeal Brief, emphasis in Appellants' original remarks).

However, the prior art already suggested injection of SRP proteins in-ovo to vaccinate birds. The ordinary artisan, having the combination of references before him or her would have been motivated to inject SRP into poultry eggs with sustained/release matricies during the times as

indicated by Appellants' claims because the ordinary artisan could infer from the prior art that sustained/release matricies delivered at the claimed times and formulated to release within the times recited by the claims would have successfully vaccinated poultry. The unpredictability asserted by Appellants is unsubstantiated and unverified and absent from the closest prior art to the claimed invention. Appellants did not disclose that they encountered any of the newly proposed problems in their disclosure and thus did not subsequently proffer solutions to overcome such problems.

Appellants assert that the Examiner ignored "...the biological consequence of providing a sustained release implant *in-ovo*...". However, the Examiner was unaware of such a consequence because such information is not found within the prior art documents cited. The prior art specifically suggests the use of *in-ovo* injection as a means to deliver SRP proteins. The combination of references provides good indication that injection of SRPs *in-ovo* will provide for vaccination of poultry. There are no teachings in the closest prior art of record, nor in the present Specification of what Appellants' now propose was a problem in the art concerning injection of SRP into poultry eggs.

Appellants' assertion that "[T]he prior art already recognizes the use of SRPs for vaccination into poults as well as in-vivo [sic] via use of sustained delivery matrices." (Final Office Action, page 13). The prior art fails to recognize the use of SRPs for vaccination in ovo using sustained delivery matrix implanted into eggs having maternally-derived antibodies to an immunogen released by the implant" is not found convincing. If the Examiner did state that it was known to deliver SRPs *in-ovo* with sustained/release delivery matricies, this was an inadvertent error as the prior art does not

explicitly teach as such. However, although the prior art does not explicitly teach *in-ovo* injection with use of sustained/delayed release matricies, the ordinary artisan, having the above cited references before him or her would have been motivated to use sustained/delayed release matricies for SRP in-ovo injection during the times indicated by the claims because first, the ordinary artisan would have recognized that SRP proteins were not advantageously given as a full vaccine prior to a time when maternal antibodies were reduced; secondly, the ordinary artisan would have been motivated to use delayed release to release the SRP entirely within such a time as 21 days or 60 days as already provided for by the prior art and third, the ordinary artisan would have been appraised that sustained release was actually advantageous due to the fact that sustained release during a time when maternal antibodies are present actually strengthens the overall vaccination response. This is the opinion of the Examiner because this is what is inferred by the overall teachings of the prior art references.

Appellants further argue:

> The Examiner errs in her interpretation of the '479 and '733 patents, stating, °°The only teaching lacking between the Emery et al. patents [the °479 patent and the °733 patent] and the claimed invention is the age of the egg at vaccination. (Final Office Action, page 15). This statement is incorrect. A second difference between the teaching of the Emery et al. patents and the method of claim 34 is the presence of maternally-derived antibody to the SRP. Moreover, the difference highlighted in the statement is precisely the difference - i.e., between unhatched embryo versus day-old chick - that is responsible for the different immunological environments that the Examiner fails to recognize as creating the unpredictability recognized in the prior art.
>
> The Examiner further errs, stating, "Although neither Emery et al. patents [sic] explicitly demonstrated in-ovo [sic] vaccination of SRP proteins at the age of the egg as indicated by claims 35 and 36 for example, determining a time to vaccinate poultry eggs with known vaccines such as SRPs which were already known to be delivered in delayed/sustained release matrices at the times as required by the claims is deemed well-within [sic] the skill level of the ordinary artisan and would have been achieved through routine optimization/experimentation." final Office Action, page 16). While this may be true for methods that involve vaccinating eggs that lack maternally-derived

> antibodies to the SRPs, it is not true in the case of vaccinating eggs having maternally-derived antibodies against the SRPs because of the risk of inducing immune tolerance rather than a protective adaptive immune response.
>
> The Examiner further errs and displays confusion about the nature of Appellants' invention, stating, "The Specification as a whole appears to be solving an asserted problem of delivering an SRP protein to a young poult in such a manner as to deliver said SRP at a time when maternal antibodies are reduced." This is an incomplete understanding of not only the actual - as opposed to asserted - problem faced by those doing business in the poultry industry, but also the solution presented by Appellants. The problem further involves how to vaccinate literally thousands of animals efficiently - in both the immunological and economical sense - in the very real commercial circumstances in which the qualitative and quantitative extent to which each egg has maternally-derived antibodies against a selected immunogen such as, for example, an SRP (a) differs and (b) cannot readily be determined. Seeking immunological efficiency suggests delaying vaccination until maternal antibodies in the chicks wane and can no longer interfere with the chicks' ability to generate an adaptive immune response at the economical expense of knowing that some chicks will be susceptible to infection. Seeking economical efficiency suggests vaccinating the animals as few times as necessary and while the vaccines are easiest to handle. However, doing so risks (a) interference by maternal antibodies with the induction of an adaptive immune response to the vaccine and (b) the induction of immune tolerance against the selected immunogen. (pp. 15-16, Appeal Brief)

Appellants' statement that the Emery et al. patents fail to teach that maternal antibody would be present is, in the opinion of the Examiner, counterfactual taking the Emery et al. patents into consideration. Claim 34 states "...wherein the egg comprises maternal antibody to the selected immunogen..." Emery et al. '733 teach that maternal antibodies are present *in-ovo*: "In mammals, a fetus receives maternally-synthesized antibodies while in utero which confers passive protection to the fetus. In the avian species, immunity is transferred from the hen via the egg, and the progeny in the first few months of life are protected against toxins, viruses and pathogenic bacteria. " (*Id.*). Hence, the egg proposed to be injected by Emery et al. '479 would have been expected to contain maternal antibodies. Again, Example 2 shows wherein a sustained/delayed release formulation of SRP is administered to 1 day old turkey poults to establish immunity against the SRP indicative of an adaptive immune response. Thus, it was recognized in the prior art that the maternal antibodies to

the selected immunogen used for vaccination must be sufficiently reduced in the poultry in order to ensure successful vaccination.

Again, Appellants' arguments regarding the unpredictability of in-ovo injection are, in the opinion of the Examiner, not found persuasive because said arguments are unsubstantiated.

Appellants' statement that the Examiner erred in interpreting the specification is not found convincing. The Examiner was merely stating her opinion of the teachings of the Specification in a general sense. The Examiner appreciates the breadth of Appellants' disclosure and again reiterates that Appellants' specification proffers challenges that were present in the prior art prior to Appellants' invention, but in the opinion of the Examiner, these problems were already recognized and solved by the teachings of the prior art. Appellants disclose specific times of inoculation of vaccines in sustained/delayed release matricies into eggs but do not specifically disclose that there would be unpredictability surrounding their methods. The unpredictability proposed by the Disclosure appears to be, in the Examiner's opinion, the same unpredictability already disclosed by the prior art; that vaccination of poultry against an antigen when maternal antibodies to the antigen are present in the poultry pose a problem. This problem was already solved by the prior art by providing vaccines with sustained/delayed matricies. There are no other solutions within the Disclosure that the Examiner can find that solve any problem that was not already solved by the teachings of the prior art.

> Appellants' solution permits vaccination at a single time with a sustained release implant so that each vaccine can receive the same vaccination and the chick will be immunologically protected regardless of when maternal antibodies against the SRP - if present at all - wanes. To this extent, Appellants' solution is similar to that described in the '733 patent. Appellants' solution goes further, however. Appellants' solution involves doing so prior to hatching, when the unhatched eggs are easier to handle than hatched chicks and in the face of the risk of inducing immune tolerance created by the combination of exposing the embryo in ovo to immunogens against which the embryo carries maternally-derived antibodies.
>
> The Examiner asserts that "[t]he prior art already recognized that the presence of maternal antibodies in young poultry hastened the need for delivery of vaccines at a time when maternal antibodies in the poultry were reduced." (Final Office action, pages 17-18). Once again, this statement oversimplifies the problem facing those in the poultry industry and the solution provided by Appellants. Appellants do not dispute that the prior art described a need to provide immunological protection to young poultry when maternal antibodies against a selected immunogen are reduced. However, the prior art fails to recognize that one could do so by vaccinating in ovo even in the presence of maternal antibodies against the selected immunogen, when the immunological developmental stage of the embryo creates a level of risk of inducing immune tolerance that is greater than when the very same vaccine is used to vaccinate hatched chicks.
>
> Thus, the method recited in claim 34 is more than the combination of familiar elements according to known methods to yield no more than predictable results. Indeed, the method of claim 34 combines certain known elements in a way that the prior art suggests could lead to precisely the opposite result - i.e., immune tolerance to the selected immunogen.
>
> As explained above, the biological and immunological reality is more complex than simply moving the time of providing the implant ahead by two days. To reiterate: because of the difference in the immunological environment of an unhatched embryo and a one-day old hatched chick, it was unpredictable whether providing a sustained release implant containing an SRP would, on the one hand, induce adaptive immunity against the SRP as described in the '733 patent when the implant is provided one day after hatching or, on the other hand, induce immune tolerance against the SRP. (pp. 16-17, Appeal Brief)

Appellants' statement that their invention would permit "...vaccination at a single time with a sustained release implant so that each vaccine can receive the same vaccination and the chick will be immunologically protected..." would be expected due to the teachings of the prior art which already disclosed this principle when carrying out sustained/delayed release of vaccines such as SRPs. Appellants state that their invention further goes beyond that of the teaching of the combination of prior art because of the ease of handling eggs as opposed to hatch chicks.

Appellants' statement that "...the prior art fails to recognize that one could do so by vaccinating in ovo even in the presence of maternal antibodies even in the presence of maternal

antibodies against the selected immunogen, when the immunological developmental stage of the embryo creates a level of risk...." is not found persuasive because the prior art already recognized the advantageous nature of in-ovo inoculation:

> The desirability of injecting materials into avian eggs during incubation has been recognized for some time. Initially, the purpose of injecting eggs was to prepare various vaccines using the egg as a growth medium for the vaccine. More recent developments have involved injecting live embryonated eggs for the purpose of accomplishing some beneficial or therapeutic effect on the embryo or the bird that eventually hatches from the egg. Such beneficial effects include increased growth, disease resistance due to in ovo vaccination, increased percentage hatch of multiple incubated eggs, and otherwise improved physical characteristics of hatched poultry. (Phelps et al. ¶ 1 under 'Background of the Invention).

Although the cited prior art does not explicitly state Appellants' assertion; i.e., that eggs are easier to handle than chicks, this would have been an obvious observation and thus an obvious advantage. Further, not only was egg-injection known at the time the Invention was filed, but injection of SRPs into eggs was already suggested by the prior art.

Appellants' argument pertaining to " because of the difference in the immunological environment of an unhatched embryo and a one-day old hatched chick, it was unpredictable whether providing a sustained release implant containing an SRP would, on the one hand, induce adaptive immunity against the SRP as described in the '733 patent when the implant is provided one day after hatching or, on the other hand, induce immune tolerance against the SRP" is not found convincing to the Examiner because, no such unpredictability was disclosed in the Specification as filed. Appellants did not provide for any information regarding the unpredictability surrounding injection of SRP into eggs at the time the Invention was made. While there is an acceptable amount of unpredictability regarding the immune functions of

poultry embryos, if there were unpredictability in the art regarding this immunity, the unpredictability would still exist in this application because there is no indication in the Instant specification that Applicants' have achieved any result which was not already expected by the prior art. Applicants' only example regarding *in-ovo* inoculation merely quantitated live births and evaluated the injection sites. Applicants did not state exactly how the biocompatible matrix was prepared for this example (i.e., a determined release time), did not measure the maternal antibody titers of the eggs, did not measure antibody titers of the chicks after hatching and thus did not evaluate the overall success of a 20 day old egg vaccination. Nor did Applicants provide any comparative data which would demonstrate that an egg at day 20 of incubation would provide for any result which would not be expected by the prior art (i.e., vaccination). It appears that this example, Example 4 in the Specification; the only example in the Specification pertaining to *in-ovo* vaccination; was set forth to assess the toxic nature of the injection itself, as there is no subsequent data at all concerning these inoculated eggs. Hence, even considering if there is unpredictability in the art with regard to vaccination of poultry eggs 1) the prior art taught vaccination of poultry with SRPs using sustained/delayed release matricies, 2) the prior art taught the advantageous nature of delivering SRP proteins in biocompatible sustained/delayed release matricies to deliver SRP proteins to poults when decreased maternal antibodies were present 3) the prior art suggested *in-ovo* vaccination of birds with SRPs 4) *in-ovo* vaccinations were routine in the art 5) *in ovo* vaccinations were successfully achieved by injecting antigens at the times recited by the claims (Evans et al.) 6) sustained delivery of SRPs was found to be advantageous even in the presence of circulating maternal antibodies and 7) delayed release times such as 21 and 60 days after hatching were

already known to be advantageous times to fully deliver the vaccine in turkey as these examples in Emery et al. ('733) were demonstrated to be successful (further, Emery et al. '733 taught that the implant could be formulated to release over a period of about 1-90 days).

While it is not improper for Appellants to provide arguments supporting their contention that the prior art would not be enabled due to the unpredictability surrounding the claimed methods at the time the Invention was made even if such indication was not provided by the prior art/Appellants' specification, the assertions made by Appellants are unsubstantiated and such assertions are not supported by the prior art nor the specification. Again, it is the opinion of the Examiner that there will be an amount of unpredictability surrounding vaccination of poultry eggs, but considering the teachings of the prior art, the ordinary artisan would have had a reasonable expectation of success in carrying-out the claimed method.

Hence, again, it is the opinion of the Examiner that Appellants' invention is an obvious modification of the prior art which could have been achieved through routine experimentation using parameters already suggested by the prior art.

Appellants' arguments pertaining to claims 69 and 84 (respectively) (pp. 18-20, Appeal Brief) are essentially the same as Appellants' arguments pertaining to claim 34 and hence, were already discussed by the Examiner, *supra*.

Appellants argue that the Evans et al. '438 patent does not cure the deficiencies of the rejection set forth under 35 USC 103(a) due to Appellants' arguments *supra* regarding the asserted patentability of claim 34 (pp. 21-22, Appeal Brief). However, it is the opinion of the Examiner that the rejection of claims 34, 37, 39-43, 67-69, 83-86, 89, 91-95 and 97-102 under 35 U.S.C. 103(a) as being unpatentable over Emery et al. (US 5,538,733) in view of Emery et al. (US 5,830,479) in view of Phelps et al. (US 5, 339,766) is not improper and hence, subsequently, the Examiner respectfully does not agree with Appellants' contention that the addition of Evans et al. does not cure the deficiencies of the rejection instituted using Emery et'al. '733 in view of Emery et al. '479 and Phelps et al. '766.

Hence, if the Examiner had reason to believe that the claimed composition was unpredictable, the claims themselves would be rejected under 35 USC 112 First paragraph, because if a large degree of unpredictability existed, Applicants' specification would not cure this deficiency considering the lack of teachings in the Specification with regard to in-ovo inoculation. Nevertheless, it is taken from the prior art as a whole that the claims are enabled because the prior art already taught successful vaccination of young poultry with SRP proteins via use of a biocompatible matrix designed to provide sustained/delayed release until a time when maternal antibodies were sufficiently reduced so the bird could mount an immune response to the immunogen (SRPs) and because SRPs delivered in such matricies were specifically suggested for in-ovo administration. Considering the breadth of information concerning poultry vaccination

with SRPs, the prior art is deemed enabling and the artisan would have had a reasonable expectation of success in carrying out the claimed invention.

Thus, absent any evidence of an unexpected result, the claimed invention is deemed an obvious variation of the methods already suggested by the prior art teachings. The ordinary artisan, relying on the above-cited US Patents would have had a reasonable expectation of success in producing the claimed method. Although neither Emery et al. patents explicitly demonstrated *in-ovo* vaccination of SRP proteins at the age of the egg as indicated by claims 35 and 36 for example, determining a time to vaccinate poultry eggs with known vaccines such as SRPs which were already known to be delivered in delayed/sustained release matricies at the times as required by the claims is deemed well-within the skill level of the ordinary artisan and would have been achieved through routine optimization/experimentation. The Specification as a whole appears to be solving an asserted problem of delivering an SRP protein to a young poult in such a manner as to deliver said SRP at a time when maternal antibodies are reduced. However, it appears that the problems asserted by the Specification *were already solved by the teachings of the prior art US Patents*. There is nowhere in the Specification which suggests that the time of vaccination is particularly crucial or where these times were found to achieve a superior result. The prior art as well as the claims teach a broad window for sustained/delayed release of the SRP antigen to deliver to a poultry; this is because it appears that there is no absolute time which is known when maternal antibodies will be at the lowest level to ensure maximum protection since this time would vary from bird to bird. Absent such additional information which would demonstrate that Applicants have achieved a result which was not already found predictable

based upon the combination of the prior art teachings; it is the opinion of the Examiner that the vaccination times were an obvious choice based upon the consideration that eggs were routinely vaccinated at these times. In the opinion of the Examiner, Appellants are claiming a method which was already suggested by the prior art and it does not appear that Appellants have gone above-and-beyond what was already known and expected from SRP vaccination of poultry as disclosed by the prior art to create a method having unobvious differences from the suggested method of the combined teachings of the prior art.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Patricia Leith

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